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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/700,879	11/20/2000	Tatsuya Tamura	TAMURA-5	4195

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EXAMINER
MAIER, LEIGH C

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 06/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/700,879	TAMURA ET AL.	
	Examiner	Art Unit	
	Leigh C. Maier	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,5-11,17,18 and 22-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,5-11,17,18 and 22-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 6, 2006 has been entered.

Claims 1, 2, 4, 12-16 and 19-21 are canceled. Claims 3, 5-11, 17, 18 and 22-24 are currently amended. Claims 26-31 are newly presented. Claims 3, 5-11, 17, 18 and 22-31 are pending. Any rejection or objection not expressly repeated has been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant's arguments with respect to the claims have been considered but are moot in view of the new grounds of rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 27 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contains subject matter that was not described in the

specification in such a way as to reasonably convey to one skilled in the relevant art that Applicant, at the time the application was filed, had possession of the claimed invention.

New claim 27 recites the limitation wherein the therapeutic agent is first bonded to the spacer, and then the spacer is bonded to the carboxyl group of HA. The examiner does not find support for this limitation.

Claim Rejections - 35 USC § 103

Claims 8, 11, 17, 18 and 22-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Khan et al (WO 96/35721) and Sakurai et al (Glycoconjugate J., 1997) in view of Akima et al (US 5,733,891).

Khan teaches the preparation of pharmaceutically active compounds, such as predinisone—prodrug of antirheumatic, predinisolone—conjugated to hyaluronic acid via a linker or "spacer arm." See abstract and example 6. The use of a spacer allows for the introduction of a greater amount of the therapeutic agent into the HA. The reference further teaches the administration of such conjugates for the treatment of joint disorders. See reference claim 9 and pages 4 and 5. The reference teaches the use of HA molecular weights of about 30 kD to 760 kD, with 130 kD being exemplified in the predisone example. See page 11, lines 5-9. Finally, it is noted that HA is not only a drug vehicle; it also has therapeutic activity in the treatment of joint disorders, such as rheumatoid arthritis. See paragraph bridging pages 1 and 2. The reference does not teach a conjugate wherein the spacer is attached to a HA carboxyl via an amide bond.

Sakurai teaches that an SOD-HA conjugate is effective in suppressing adjuvant arthritis in rats, a mode for chronic rheumatoid arthritis in humans. See abstract and last paragraph of the reference.

Akima teaches the preparation of conjugates of therapeutic agents bonded to a HA carboxyl via amide bonding. See abstract. The reference further teaches the preparation of the conjugates by preparing an activated ester of HA, followed by addition of a therapeutic agent, with or without a spacer. See example 2. This example discusses how reaction conditions may be varied depending on the particular physico-chemical properties of the reactants. The reference specifically suggests the preparation of a prednisolone conjugate. See col 3, lines 9-12.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to administer a conjugate of HA and a therapeutic agent as recited in the claims for the treatment of joint diseases. Khan and Sakurai had established that drug-HA conjugates have utility for the treatment of such diseases. In the absence of unexpected results, one of ordinary skill would reasonably expect that any drug (having known utility for treating joint diseases) conjugated to HA in any known fashion would have this same activity. Therefore, the artisan would reasonably expect success in using such a conjugate for the treatment of joint disorders. Although Akima is directed at the treatment of cancer, these references are analogous because one of ordinary skill, in possession of Khan and/or Sakurai, would be motivated to look to the art regarding HA-conjugates, in general, and not just ones having the stated utility of treating joint disorders.

With respect to the preparation, the use of activated esters for the preparation of HA amides is known in the art and discussed in Akima. In preparing a conjugate of species A and

species B, wherein the two species are connected through a spacer arm, one of ordinary skill would be faced with the choice of preparing A-linker or B-linker first. In the absence of unexpected results, it would be within the scope of the artisan to select either as the first step in a process of preparing A-linker-B. Applicant has demonstrated no criticality in any such preparation step. Finally, it would be within the scope of the artisan to optimize the amount of the therapeutic agent by weight in the conjugate through routine experimentation.

With respect to the supposed unexpected results demonstrated by Figs. 6 and 7, Applicant notes that the conjugated drug is retained longer than the unconjugated one. However, no determination is made with respect to the retention of HA, *per se*. Without this information, no determination of unexpected results can be made.

Claims 3, 5-7, 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Khan et al (WO 96/35721) and Sakurai et al (Glycoconjugate J., 1997) in view of Akima et al (US 5,733,891) as applied to claims 8, 11, 17, 18 and 22-31 above, and further in view of Gallardy et al (WO 92/09563).

Khan, Sakurai and Akima teach as set forth above. The references do not teach the use of MMP inhibitors.

Gallardy teaches hydroxamic acid-based MMP inhibitors, as discussed in previous Office actions. The reference teaches that the MMP inhibitors have utility for the treatment of such disorders as tumor metastasis and rheumatoid arthritis. See page 10, lines 12-18. The inhibitors recited in the claims are within the scope of the inhibitor designated as formula (1) in Gallardy. See pages 3-5.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare and administer an MMP inhibitor conjugated to HA via an amide linkage for the treatment of joint disorders. As discussed above, Khan and Sakurai had established that drug-HA conjugates have utility for the treatment of such diseases. In the absence of unexpected results, one of ordinary skill would reasonably expect that any drug (having known utility for treating joint diseases) conjugated to HA in any known fashion would have this same activity. Therefore, the artisan would reasonably expect success in preparing and administering an HA conjugate with an MMP inhibitor, such as those taught by Gallardy, because the reference teaches that these compounds have utility in the treatment of joint disorders. In the absence of unexpected results, it would be within the scope of the artisan to select any known method, such as that taught by Akima, for the preparation of such a conjugate. It would further be within the scope of the artisan to determine the optimum weight percent of the MMP in such a conjugate through routine experimentation.

Examiner's hours, phone & fax numbers

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leigh Maier whose telephone number is (571) 272-0656. The examiner can normally be reached on Tuesday, Thursday, and Friday 7:00 to 3:30 (ET).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Anna Jiang (571) 272-0627, may be contacted. The fax number for Group 1600, Art Unit 1623 is (571) 273-8300.

Visit the U.S. PTO's site on the World Wide Web at http://**www.uspto.gov**. This site contains lots of valuable information including the latest PTO fees, downloadable forms, basic search capabilities and much more. Information regarding the status of an application may be obtained from the Patent Application Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished application is available through Private PAIR only. For more information about the

PAIR system, see http://pair-direct.uspto.gov Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197.

Leigh C. Maier
Primary Examiner
May 26, 2006